Reversible dementia and gait disturbance after prolonged use of valproic acid

Matthew D. Evans⁴, Ron Shinar⁵, Roy Yaari¹,²,³,⁶

¹ University of Arizona College of Medicine, Phoenix Campus, 550 East Van Buren Street, Phoenix, AZ 85004, USA
² Banner Good Samaritan Medical Center Department of Medical Imaging, 1111 E McDowell Rd, Phoenix, AZ 85006, USA
³ Banner Alzheimer’s Institute, 901 E Willetta St, Phoenix, AZ, 85006, USA

Case

A 65-year-old woman with a generalized seizure disorder which began at age 25 presented to a Memory Disorders Clinic complaining of confusion and difficulty walking. Since valproic acid (VPA) was initiated approximately at age 50 she has been seizure-free with an average daily dose of 1 g

Incidentally, the patient has a history of gradual hearing loss of unknown etiology starting in her early 50s. Her mother and maternal uncle also had a similar pattern of hearing loss. The same maternal uncle has a C8393TT-Pro +1→G mutation, which would explain the highly variable clinical timeline of symptom appearance. The patient’s hearing loss and epilepsy are suggestive of a mitochondrial DNA (mtDNA) mutation. Unfortunately, in our patient genetic testing was not performed.

VPA and ammonia levels were therapeutic and normal, respectively. A brain MRI revealed mild prominence of the lateral ventricles concerning for normal pressure hydrocephalus, however significant sulcal atrophy was also observed.

VPA was changed to levetiracetam without incident. Cognition and gait disturbance gradually normalized over the following two months. A brain MRI 4 months after cessation of VPA showed possible, but not significant, reduction of ventricular size (see table 1).

Methods / Results

As dementia and gait disturbance in an elderly patient could be due to a wide variety of causes, her clinical history was evaluated with the Naranjo adverse drug reaction (ADR) scale. This scale determines the probability that a patient’s clinical syndrome is related to an ADR in a more objective manner than clinical judgment alone. The likelihoods are reported quantitatively with an associated qualitative modifier for score ranges, which include: “definite (9 or more), probable (5-8), possible (1-4), doubtful (0)”. This patient scored a 5, indicating an ADR to VPA is probable.

The specific questions of the Naranjo ADR questionnaire are:

“Did the ADR improve when the drug was discontinued or a specific antagonist was given? Yes, +1

Was the ADR more/severe when the dose was increased/decreased? Yes, +1

Are there previous conclusive reports on this reaction? Yes, +1

Did the ADR appear after the suspected drug was given? Yes, +2

Was the ADR confirmed by any objective evidence? Yes, +3

Did the ADR appear when the drug was readministered? No, -1

Are there alternative causes that could have caused the ADR? Yes, -1. NPH may have caused the patient’s symptoms despite a negative large volume LP, though unlikely

Did the ADR reappear when a placebo was given? No, -1

Was the drug detected in any body fluid in toxic concentrations? No, +0

Did the patient have a similar ADR to the same or similar drugs in any previous exposure? No, +0

Discussion

A proposed mechanism of the reversible cognitive decline seen in these patients taking VPA is a mitochondrial DNA (mtDNA) mutation. One of the reported cases of VPA-induced non-hyperammonemic reversible cognitive decline describes a pediatric patient who was found to have a C8393TT-Pro +1→G mutation in the MTATP8 gene. Also, since mtDNA mutations are heteroplasmy, it would explain the highly variable clinical timeline of symptom appearance. The patient’s hearing loss and epilepsy are suggestive of a mtDNA mutation syndrome, especially with her family history of similar symptoms that followed a maternal inheritance pattern. Unfortunately, in our patient genetic testing was not performed.

Evidence indicates that GABA mediates (GABA) and it is an antagonist of the human brain GABA-degrading enzyme. Thus, VPA may cause a transient inhibitory effect on dopaminergic pathway.

VPA has also been shown to reversibly inhibit neurite outgrowth in a cellular study.

Conclusion

This case exemplifies one of the adverse effects of VPA, which can cause reversible neurological symptoms even in long-term treated patients. Clinicians should be aware of how valproate-induced cognitive impairment and gait disturbance can masquerade as dementia syndromes such as Alzheimer’s disease or normal pressure hydrocephalus, especially when pseuodobulbar symptoms are present. Recognizing this clinical scenario can allow clinicians to avoid unnecessary tests or treatments, and possibly reverse the condition.

Table 1 Ventricular measures before and after cessation of VPA. On 3 out of 4 measures of ventricular size, numeric reductions were seen 4 months after cessation of VPA. The ventricular measurements were performed by a radiologist blinded to the clinical history.

Table: | Measure 1: transverse diameter between lateral most portions of the frontal horns of the lateral ventricles at the level of the head of caudate by axial plane. | Measure 2: transverse diameter of the frontal horns of the lateral ventricle by coronal plane at the level of the hypophysis. | Measure 3: greatest anteroposterior diameter of the right lateral ventricle by sagittal plane. | Measure 4: greatest anteroposterior diameter of the left lateral ventricle by sagittal plane. |
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>57 months prior</td>
<td>41.4</td>
<td>37.1</td>
<td>76.8</td>
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<tr>
<td>21 months prior</td>
<td>42.1</td>
<td>41.3</td>
<td>80.3</td>
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<td>7 months prior</td>
<td>43.0</td>
<td>43.2</td>
<td>82.2</td>
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<td>4 months after</td>
<td>43.5</td>
<td>41.4</td>
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p-values: 1 = 0.29; 2 = 0.83; 3 = 0.67; 4 = 0.73. No statistically significant change after VPA cessation.

References

5. Gale RE. Role of the subclinical form in GABA-mediated anticonvulsant actions. Adv Neurol 1986;41:63-44.